REMARKS

This paper is responsive to the Office Action mailed October 6, 2003. The present application was originally filed with Claims 1-14. In a preliminary amendment filed July 10, 2001 Applicants cancelled original Claims 1-14 and submitted new Claims 15-34, which substantially corresponded to the original claims but were written in proper claim format for review in the United States Patent Office. Included in the preliminary amendment was Applicants' amendment of the specification to include the statement cross-referencing the related applications required by 37 C.F.R. §1.78.

Response to issues presented under obviousness-type double patenting

Claims 15-34 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 1, 17, 19-21, 26, 27 and 32-34 of U.S. Patent No. 6,084,091. Specifically, the Examiner contends that although the claims are not identical, they are not patentably distinct because the claims of the '091 patent allegedly anticipate the claims of the present invention. The Examiner contends:

> "The '091 patent teaches a method of purifying nucleic acids in a biological sample, including stool, comprising providing an extraction buffer and contacting the sample with an adsorption matrix comprising a carbohydrate or potato flour." (Office Action, page 3.)

Applicants respectfully traverse. The '091 patent teaches a method of purifying, stabilizing, and isolating nucleic acids in a biological sample, including stool, wherein an adsorption matrix is added to the nucleic acid containing biological sample in order to bind contaminants. The adsorption matrix may be added directly to the sample, or the sample may be homogenized in a buffer and then contacted with the adsorption matrix. By using the inventive method taught in the '091 patent, substances which either contaminate or damage the nucleic acids, or inhibit the enzymatic manipulation thereof, are largely removed, allowing extended storage times for the nucleic acids.

In contrast, the present invention involves the discovery that the nucleic acid isolation processes described in the above Muller references are more effective when combined with the particular buffer solutions described in the present application. Because the claimed method utilizing the novel buffer

solutions is patentably distinct from the cited reference, i.e., the use of the buffer in the method resulted in a surprisingly unexpected increase in efficiency, the claims of the present invention are patentably distinct from the teaching of the '091 patent.

For example, Applicants teach that using an extraction buffer having: an acidic to neutral pH, with a pH of 2-8 being particularly preferred; a high salt concentration, with a concentration of 100mM or greater being preferred; and a phenol-neutralizing substance, e.g., polyvinylpyrrolidone, β-mercaptoethanol and dithiothreitol. Extraction buffers containing the above ingredients were neither taught nor suggested in the '091 patent, which teaches extraction buffers:

> "[S]uitable to take up a specimen containing nucleic acids is a buffer system based on tris-HCL pH 8.5-9.5, EDTA and maybe NaCl. A particularly preferred buffer, especially for taking up stool specimens, contains 500mM (=500 mmol/l) tris-HCL pH 9, 50 mM EDTA and 10mM NaCl." (U.S. Pat. No. 6,084,091, column 5, lines 9-14.)

Moreover, Applicants present direct comparison evidence showing the surprisingly dramatic increase in the amplificability of the DNA isolated from stool when substituting the extraction buffer of the '091 patent with the extraction buffer taught in the present application, *see, e.g.* Examples 1 and 2 of Applicants' specification.

Incorporation of the extraction buffer taught in the present application into the DNA isolation method resulted in a surprisingly unexpected increase in efficiency. Therefore, the claims of the present invention are patentably distinct from the claims of the '091 patent.

Response to issues presented under 37 U.S.C. §102(b)

Claims 15-17, 19-30 and 32-34 stand rejected under 35 U.S.C. §102(b) as being allegedly anticipated by the publication (in German) of the international application PCT/EP96/03595 (WO 97/07239). Applicants still await the English translation of the cited reference, therefore Applicants base their response on the Examiner's contention that U.S. Pat. No. 6,084,091 is equivalent to WO 97/07239.

As discussed above, the '091 patent teaches a method of purifying, stabilizing, and isolating nucleic acids in a biological sample, including stool, wherein an adsorption matrix is added to the nucleic acid containing biological sample in order to bind contaminants. The adsorption matrix may be added directly to the sample, or the sample *may* be homogenized in a buffer and then contacted with the adsorption matrix. By using the inventive method taught in the '091 patent, substances which either contaminate or damage the nucleic acids, or inhibit the enzymatic manipulation thereof, are largely removed. The present invention, on the other hand, involves the discovery that the nucleic acid isolation processes described in the above Muller references are more effective when combined with the particular buffer solutions described in the present application.

A rejection for anticipation under 35 U.S.C. §102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference. *See* MPEP §2131. Because the reference of record fails to disclose or suggest aspects of the invention that are particularly and distinctly claimed, reconsideration and withdrawal of the rejection under 35 U.S.C. §102 are requested.

Applicants teach a method for isolating nucleic acids from a biological sample using an adsorption matrix and an extraction buffer having: an acid to neutral pH, with a pH of 2-8 being particularly preferred; a high salt concentration, with a concentration of 100mM or greater being preferred; and a phenol-neutralizing substance, e.g., polyvinylpyrrolidone, β-mercaptoethanol and dithiothreitol.

Although the '091 mentions that buffer solutions may be incorporated into the nucleic acid purification method, extraction buffers containing the above ingredients were neither taught nor suggested in the '091 patent. In fact, the '091 patent teaches away from the present invention, suggesting the use of solutions with a higher pH and low salt concentrations:

> "[S]uitable to take up a specimen containing nucleic acids is a buffer system based on tris-HCL pH 8.5-9.5, EDTA and maybe NaCl. A particularly preferred buffer, especially for taking up stool specimens, contains 500mM (=500 mmol/l) tris-HCL pH 9, 50 mM EDTA and 10mM NaCl." (U.S. Pat. No. 6,084,091, column 5, lines 9-14.)

Therefore, because WO 97/07239 fails to teach or suggest aspects of the invention as particularly and distinctly set forth in the claims, Applicants request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b).

Response to issues presented under 35 U.S.C. §103(a)

Claims 18 and 31 stand rejected under 35 U.S.C. §103(a) as unpatentable over Muller et al. (Applicants note that it is unclear which Muller et al. reference the Examiner is referring to, therefore Applicants assume the Examiner refers to WO 97/07239 and Applicants base their response on the Examiner's contention that U.S. Pat. No. 6,084,091 is equivalent to WO 97/07239.) Specifically, the Examiner contends that Muller et al. teaches:

> "the method as described above, but also teach various polymer carriers as well, such as polyvinylidene chloride, polyethylene, polypropylene and polyethylene, for example. See page 8. Muller et al. fail to teach the specific polymer polyvinylpyrrolidone.
>
> It would have been obvious to one of skill in the art at the time the invention was made to use polyvinylpyrrolidone as a carrier in the present method. Muller et al. teach a variety of anionic polymers which can have modified with functional groups for use in the present method. Polyvinylpyrolidone is a known anionic polymer. One of skill in the art would have been motivated to use this polymer in the present method because it shares qualities and characteristics of those already disclosed by Muller et al. Moreover, it is well within the purview of the ordinary skilled artisan to modify amounts and concentrations of known substances such as carriers, salts or pH. Thus, one of skill in the art would have been motivated to optimize the amounts of polyvinylpyrrolidone carrier in the method. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made." (Office Action, page 4.)

Applicants respectfully traverse. MPEP §2143.03 states that "[t]o establish prima facie obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art." (emphasis added). It is essential, therefore, to consider all the elements of the claimed invention. Because the cited references fail to disclose or suggest the methods of Claims 1 and 33 *as a whole*, reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) are respectfully solicited.

The present invention involves the discovery that the nucleic acid isolation processes described in the above Muller references are more effective when combined with the particular buffer solutions described in the present application. The Muller references do not teach nor suggest the use of extraction buffers having an acidic to neutral pH, a high salt concentration, and a phenol-neutralizing substance. In fact, Muller et al. teaches away from the present invention, suggesting the use of buffers with a high pH and a low salt concentration. Moreover, the present extraction buffers and their use are not obvious variants over Muller et al. because use of the extraction buffers taught by the Applicants showed unexpected results, that is, a surprisingly increase in efficiency in the nucleic acid purification method. This surprising result is demonstrated in Applicants direct comparison evidence showing the dramatic increase in the amplificability of the DNA isolated from stool when substituting the extraction buffer of the '091 patent with the extraction buffer taught in the present application. (*See, e.g.* Examples 1 and 2 of Applicants' specification.) Additionally, Applicants point out that Muller et al. teach the use of synthetic polymers such as polyvinylidene fluoride (which the Examiner considers to be an equivalent to polyvinylpyrrolidone) as organic carrier substances, not as a phenol-neutralizing substances as disclosed in the present application.

Therefore, since Muller et al. fail to disclose or suggest the presently claimed invention in Claims 15 and 28 *as a whole*, they cannot sustain an obviousness rejection under 35 U.S.C. §103(a). Moreover, because independent Claims 15 and 28 (from which Claims 18 and 31 ultimately depend) are non-obvious, Claims 18 and 31 cannot be found obvious under 35 U.S.C. §103 as a matter of law. MPEP §2143.03

In view of the foregoing remarks, reconsideration and allowance of the claims as amended are respectfully requested.

Respectfully submitted,

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